REMARKS

Claims 1-20 are pending in the instant application. The Claims are subject to a restriction requirement under 35 U.S.C. §121. Claims 1-7 and 12-20 are now being examined and have been rejected for the reasons noted hereinbelow. Applicants have cancelled Claims 1-11 and 20 without prejudice. Applicants respectfully traverse the Restriction Requirement and the rejections as set forth by the Examiner and request reconsideration of the application in light of the amendments hereinabove and the following remarks.

The Examiner requires restriction of the application to one of the following sets of claims directed to distinct inventions:

Group I: Claims 1-7 and 12-20 drawn to oligopeptides and conjugates; and
Group II: Claims 8-11, drawn to an assay.

Applicants hereby elect, with traverse, the invention described in Group I, namely claims directed at peptides that can be selectively proteolytically cleaved by free PSA and cytotoxic conjugates that comprise such oligopeptides that are useful in the treatment of prostate cancer.

Applicants initially note that an accurate and scientifically based characterization of all of the inventions of the instant application is as peptides that are catalytically cleaved by enzymatically active PSA, and therapeutic and analytical uses of such peptides. Applicants contend that regardless of whether a claim is directed to those novel PSA cleavage site containing peptides, or the assay or conjugate that comprises the peptides, all of the claims share the feature of the oligopeptides that are selectively cleaved by PSA. Applicants contend that a search of the prior art which focuses on such PSA selectively cleavable oligopeptides would be comprehensive with respect to all of the instant inventions yet would not require a serious burden on the Examiner. MPEP 803 provides:

> There are two criteria for a proper requirement for restriction between patentably distinct inventions:
> (1) The inventions must be independent or distinct as claimed; and
> (2) There must be a serious burden on the examiner if restriction is not required.

Because there would be no serious burden on the Examiner in searching such closely related groups, but patentably distinct groups, Applicants respectfully contend that the restriction requirement between Groups I and II is improper.

Applicants respectfully note that the Examiner of the instant application stated on the record in an Office Action dated September 6, 1995, for Ser. No. 08/267,092 (the first priority document related to the instant application) that the peptides of the priority application and the conjugates of the priority application were not only patentably distinct from the assay claims but also patentably distinct between themselves. Applicants respectfully note that they have made decisions related to the prosecution of the '092 application, including Election of a Species and payment of an Issue Fee, based on the previous Restriction Requirement, which was made final in an Office Action dated January 25, 1996. Applicants respectfully contend that Applicants' dependence on Examiner Marshall's previous determination of distinctness within the the very same types of subject matter that the Examiner has now chosen to "re-Group" negatively impacts the instant application (for example, with respect to the below noted provisional rejections under 35 U.S.C. §101 and the judicially created doctrine of obviousness type double patenting). Therefore, Applicants respectfully contend that, not only is the Examiner's Restriction Requirement untenable because of a lack of undue burden on the Examiner, but also, the patenably distinct groups that the Examiner has now defined are improperly drawn.

Applicants note that the claims now being examined are directed to peptides that can be selectively proteolytically cleaved by free PSA and cytotoxic conjugates that comprise such oligopeptides that are useful in the treatment of prostate cancer.

Despite Applicants traversal of the Restriction Requirement, in order to advance the prosecution of the application Applicants have canceled the claims directed to the subject

matter of Group II and the claims directed to the oligopeptides (Claims 1-7) without prejudice to filing a divisional application directed to those inventions.

The Examiner has provisionally rejected Claims 1 and 5-6 under 35 U.S.C. §101 as claiming the same invention as that of copending application '092. Applicants note that Claims 1-7 have been canceled in the instant application. In light of those amendments, Applicants contend that the rejection under 35 U.S.C. §101 over the '092 application is now moot and should be withdrawn.

The Examiner has provisionally rejected Claim 1 under 35 U.S.C. §101 as claiming the same invention as that of copending application Ser. No. 08/540,412. Applicants note that Claims 1-7 have been canceled in the instant application. In light of that amendment, Applicants contend that the rejection under 35 U.S.C. §101 over the '412 application is now moot and should be withdrawn.

The Examiner has provisionally rejected Claims 2-4 under the judicially created doctrine of obviousness-type double patenting as being unpatenable over Claims 2-4 of copending application '092. Applicants note that Claims 1-7 have been canceled in the instant application. In light of that amendment, Applicants contend that the rejection under the judicially created doctrine of obviousness-type double patenting over the '092 application is now moot and should be withdrawn.

The Examiner has provisionally rejected Claims 2-7 and 12-20 under the judicially created doctrine of obviousness-type double patenting as being unpatenable over Claims 2-7 and 12-23 of copending application '412. Applicants respectfully request that this rejection, which may be overcome by the filing of a terminal disclaimer, be held in abeyance until patentable subject matter is identified in the instant application.

The Examiner has rejected Claims 1-6 under 35 U.S.C. §102(b) as being anticipated by the Lilja et al. J. Biol. Chem. reference. The Examiner notes that the claims refer to the peptides as comprising peptide sequences that are enzymatically cleaved by free PSA. The Examiner contends that such language encompasses the sequence of

semenogelin, which is disclosed by Lilja et al. Applicants respectfully note that semenogelin I and semenogelin II are specifically excluded from the oligopeptides claimed in the instant invention by language in the specification on page 9, lines 9-10. Since the scope of the claims must be read in light of the specification, Applicants respectfully contend that the exclusion of semenogelin from the claimed subject matter renders the Examiner's rejection under 35 U.S.C. §102(b) moot and request that this rejection be withdrawn.

The Examiner has rejected Claim 7 under 35 U.S.C. §103 as being unpatenable over the Lilja et al. reference in view of the discussion in the application as filed regarding acetylation of peptides. Applicants respectfully note again that the peptides disclosed by Lilja et al. (semenogelin I and II) are specifically excluded from the oligopeptides claimed in the application as filed. Applicants also note that of the sequences now claimed in Claim 7, because of the N-terminus acetylation, none of those sequences could be "comprised" in the full length sequences of semenogelin I and II, which would then be N-protected. Applicants thus contend that there is no teaching or suggestion in either the Lilja et al. article or any statement by the Applicants that the semenogelin I and II peptides should be dramatically and significantly truncated from both ends, significantly modified in most cases and then N-acetylated to provide the peptides claimed in Claim 7. Because one of ordinary skill in the art would have no motivation to make those modifications to the previously dsclosed semenogelin I and II sequences, Applicants contend that the Examiner's rejection of Claim 7 under 35 U.S.C. §103 is untenable and should be withdrawn.

The Examiner has rejected Claims 12-20 under 35 U.S.C. §103 as being obvious over the previously discussed Lilja et al scientific publication in view of the Kaneko et al. U.S. Pat. No. 5,349,066. The Examiner suggests that the disclosures in the Lilja et al reference read on the oligopeptide portion of the instant invention. As noted before, in light of the clear limitation to the limitation to the peptide component of the claimed conjugates, the Lilja et al. reference does not read on the oligopeptides of the instant claims, nor do they suggest that there are several smaller oligopeptides that are also selectively cleaved by free PSA. And, as noted by the Examiner, there is no teaching or

suggestion by Lilja et al. that any peptides, especially not truncated and significantly modified portions of semenogelin I and II, should be conjugated to a cytotoxic agent.

Applicants note that the Kaneko et al. patent describes conjugates that comprise a cytotoxic molecule linked by a bifunctional compound to a molecule that is reactive with a target cell population. Applicants note that the description in the Kaneko patent of a targeting molecule is limited to antibody proteins and ligands (col. 9, lines 29-31). Applicants note that the "antibodies" and "ligands" are described in the patent as binding to tumor associated antigens, binding to virus or other pathogen associated antigens, or binding specifically to a receptor associated with the cell surface of a target cell population (col. 11, lines 5-51). Applicants note that there is no description or suggestion in the Kaneko et al. patent that such conjugates be modified to comprise, instead of a ligand or antibody, an oligopeptide that is selectively cleaved by an enzyme that is intimately associated with the target cell population.

Applicants respectfully note that the release of the cytotoxic reagent as described in the Kaneko et al. patent depends on cleavage of an acid sensitive bond of the conjugate within the target cell (col. 12 lines 33-41). Applicants again note that the conjugates of the instant invention are selectively cleaved by enzymatically active free PSA in the vicinity of the target prostate cancer cell. Applicants respectfully contend that there is no requirement that the conjugates of the instant invention actually come into contact with acid in order to liberate the cytotoxic agent. Applicants also note that there is no suggestion by Kaneko et al. that the novel "bifunctional compounds" of their invention should <u>not</u> be present in a conjugate, as is the case with the instant invention which contains no such bifunctional compound.

Applicants finally note that there is no teaching in the Kaneko et al. patent that such inventions as disclosed therein should be combined with the teaching of Lilja et al.

Therefore, Applicants strongly content that, in spite of the description in the prior art of Semenogellin I and II and of conjugates of cytotoxic agents and targeting molecules, the conjugates claimed in the instant application that rely on selective cleavage of a

oligopeptide portion of a cytotoxic conjugate by an enzyme is not taught or suggested by those references, and a person of ordinary skill in the art would not be motivated to make such a conjugate based on those disclosures. Applicants therefore contend that the Examiner's rejection under 35 U.S.C. §103 as being obvious over the previously discussed Lilja et al scientific publication in view of the Kaneko et al. U.S. Pat. is untenable and should be withdrawn.

Applicants respectfully contend that the Examiner's objections and rejections of the instant application been addressed and obviated by the above amendments and remarks, and that Claims 12-19 as filed are allowable and an early Notice of Allowance is earnestly solicited.

Respectfully submitted,

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